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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOODWARD, CHERIE M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/256,156	GILLIES ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-8,10,27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-8,10,27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's Amendment of 21 October 2005, is acknowledged and entered. Claims 1, 4, 6-8, 10, 27, 29, and30 are pending and under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections Maintained

2. The rejection of claims 1, 6-8, 10, 27, 29, and 30, as being unpatentable over Gillies, in view of Gray, as evidenced by Ravetch, is maintained, for the reasons stated in the previous Office Actions of 21 June 2005 and 30 September 2004. Applicant's arguments, see Remarks, filed 21 October 2005, with respect to the rejection of claims 1, 6-8, 10, 27, 29, and 30 as being unpatentable over Gillies et al., (1993, Bioconjugate Chem. 4:230-235, hereinafter "Gillies") in view of Gray et al., (U.S. Patent 6,444,792, hereinafter "Gray"), as evidenced by Ravetch (1997, Cur Opin Immun, 9:121-125, hereinafter "Ravetch") have been considered but are not persuasive.

Claim 1 and depending claims (6-8, 10, 29, and 30) recite a region of a gene construct encoding an antibody-based fusion protein including, at its 5' end, nucleotides encoding at least a port of an IgG CH2 domain, with a mutation or a deletion reducing binding affinity for an Fc receptor and at the 3' end, nucleotides encoding a non-Ig protein. Claim 27 recites an antibody-based fusion protein for administration to a mammal, the fusion protein comprising a variable domain and an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody based fusion protein comprising an IgG1 CH2 domain linked to said non-Ig protein.

Applicants argue that while Gillies teaches a fusion protein in the appropriate orientation (i.e. Ig-IL-2), Gillies does not teach mutations that would increase the serum half-life of the Ig-IL-2 fusion protein. Applicants argue that Gray does not teach the mutations of his invention that result in an immunoglobulin fusion protein with an improved serum half-life. Applicants argue that there is no indication that Gray appreciated or taught that mutations to the Fc region can result in lengthened or improved serum half-lives. In his analysis, Gray compares the serum half-life of wild type CTLA4-IgG1 and a version of CTLA1-IgG4 mutated to contain the nucleotide changes in the Ch2 domain to replace amino acids thought to be required for IgG binding to Fc receptors, and complement activation (see Gray,

col 30, lines 21-29 and col 40, lines 9-39). Further, Applicants argue that Gray's data shows that the β phase half-life of wild type CTLA4-IgG1 was longer than the mutated CTLA4-IgG4, not shorter (col 40, lines 31 and 34). Thus, Applicants submit that the deficiencies of Gillies cannot be remedied by the addition of Gray.

Additionally, Applicants argue that the teachings of Ravetch, which state that Fc receptors are involved in the determination of serum immunoglobulin half-life (page 121, first column), are not analogous to the instantly claimed Fc receptors (FcR), (e.g. FcγR subtypes). Applicants argue that the Fc receptors that affect the serum half-life of antibodies, as taught by Ravetch, are FcRp/FcRn receptors and not the Fcγ receptors claimed by Applicants. Applicants arguments have been considered, but are not persuasive.

It has been well known in the art for over 40 years that the long survival of IgG relative to other plasma proteins is due, in large part, to IgG protection receptors (FcRp/FcRn). This is known as the Brambell hypothesis. The FcRp/FcRn receptor, which was identified as the same protein in 1996, (see, for example, Junghans *et al.*, May 1996 PNAS 93:5512-5516, abstract) is known to bind IgG in pinocytic vacuoles and redirect its transport into circulation. It is only when the FcRp/FcRn receptors are saturated that the excess unbound IgG then passes to unrestricted lysosomal catabolism (see *i.e.* Junghans *et al.*, p. 5512, column 1, last paragraph).

Applicants arguments with regard to Ravetch are not persuasive. Ravetch notes that extrapolation from animal studies suggests that mutations which reduce the ability of FcγRs to trigger cellular activation might correlate with protection from immune complex mediated diseases (p. 124, first column, second paragraph). Ravetch also specifically states that in studies of Lupus patients, linkages have been found which correlate with a lower affinity binding allele for FcγRIIA that relates to increased severity of glomerular disease (via excess antibody deposition in the kidneys) (p. 124, first column, second paragraph). This allelic receptor, Ravetch notes, is less efficient in binding IgG2 and IgG3 complexes. Thus, although it is well known that FcRp/FcRn receptors directly affect the circulation of IgGs, Ravetch also teaches that Fcγ receptors are involved with immunoglobulin circulation, immune complex clearance, and pathogenicity. As such, Applicants arguments with regard to Ravetch are not persuasive.

Gray *et al.*, teach CLTA4IgG4 versus CTLA4IgG1 has decreased complement activation, which would result in a longer circulating half-life (column 10: lines 60-64). Gray also teaches that modifying the CH2 domain of Cγ1 , Cγ2, Cγ3 and Cγ4 is taught to reduce "a biological effector function... Fc receptor interaction" (column 4: lines 24-28), as previously discussed in the Office Actions of 30 September 2004, 21 June 2005, and *supra*.

Gillies, Gray, and Ravetch teach all of the limitations of claims 1, 6-8, 10, 27, 29, and 30, as stated in the Office Actions of 21 June 2005 and 30 September 2004. As such, the rejection of claims 1, 6-8, 10, 29, and 30 as being unpatentable over Gillies, in view of Gray, as evidenced by Ravetch, is maintained.

3. Applicant's arguments, see Remarks, filed 21 October 2005, with respect to the rejection of claim 27 as being unpatentable over Gillies (see *supra*) in view of Gray (see *supra*), as evidenced by Ravetch (see *supra),* have been considered but are not persuasive.

Regarding claim 27, applicants argue that Gray does not teach the mutations of his invention that result in an immunoglobulin fusion protein with an improved serum half-life. Applicants argue that there is no indication that Gray appreciated or taught that mutations to the Fc region can result in lengthened or improved serum half-lives. In his analysis, Gray compares the serum half-life of wild type CTLA4-IgG1 and a version of CTLA1-IgG4 mutated to contain the nucleotide changes in the Ch2 domain to replace amino acids thought to be required for IgG binding to Fc receptors, and complement activation (see Gray, col 30, lines 21-29 and col 40, lines 9-39). Further, Applicants argue that Gray's data shows that the β phase half-life of wild type CTLA4-IgG1 was longer than the mutated CTLA4-IgG4, not shorter (col 40, lines 31 and 34). Thus, Applicants submit that the deficiencies of Gillies cannot be remedied by the addition of Gray. Applicants arguments have been considered but Are not persuasive.

Gray *et al.* teach CLTA4IgG4 versus CTLA4IgG1 has decreased complement activation, which would result in a longer circulating half-life (column 10: lines 60-64). Gray also teaches that modifying the CH2 domain of Cγl , Cγ2, Cγ3 and Cγ4 is taught to reduce "a biological effector function... Fc receptor interaction" (column 4: lines 24-28), as previously discussed in the Office Actions of 30 September 2004, 21 June 2005, and *supra.*

It was well known in the art at the time Grey was filed (earliest priority date 2 February 1996), that in amino acids of the IgG CH2 domains in IgG1, -2., -3, and –4, and characterize the binding affinities of those immunoglobulin domains with various FcγRs. See, for example, Canfield *et al.*, (J Exp Med, 1991 June 173:1483-1491). Thus, Grey would have appreciated what was well known in the art, that mutations to the Fc region can result in lengthened or improved serum half-lives.

For example, Canfield et al., teach that substitution of either Leu(234) or Leu (235) in IgG1 and corresponding amino acids in IgG3 are critical to high affinity binding. Substitution at either of those sites reduces the IgG association constant by 10-100 fold (see p. 1483, summary). Additionally, Canfield teaches that human IgG4 differs in the hinge-link region from the high affinity subclasses (IgG1 and

IgG3) at only one position: Phe replaces Leu(234) (p. 1488, column 1, second full paragraph). Thus, it would be obvious to one of ordinary skill in the art to mutate the Leu(234) in an IgG1 or corresponding IgG3 Ch2 domain in order to reduce binding affinity. One of skill in the art would reasonably expect success because the substitution occurs naturally in IgG4 that results in greatly reduced binding affinity. Moreover, Canfield teaches that IgG4 with the Leu(234) mutation exhibits increased affinity for FcγR1. However, Canfield notes that the binding affinity does not reach the level of IgG3 (p. 1488, column 1, last paragraph, and p. 1487, Table 2). In an attempt to explain why the Leu(234) mutated IgG4 doesn't reach the high affinity level of IgG1 and IgG3, Canfield looks to the hinge region, and replaces the relatively stiff IgG4 hinge region with a γ3 hinge, among others (p. 1488, column 2, last paragraph). Canfield finds that the flexibility of the hinge is not likely to play a direct role in receptor interaction, but that it exerts a conformational effect, and by controlling the spacing of the Fab and Fc regions, one can determine the accessibility of the receptor binding site on the Fc (p. 1489, column 1, first full paragraph; see also p. 1490, column 1, third paragraph). This is critically important because Canfield teaches that increasing binding affinity may require an appropriate combination of features before an observable improvement is achieved (i.e. the IgG4 Leu(234) mutation in the CH2 region plus a variable region domain) (Canfield, p. 1490, second column, last paragraph). Canfield also teaches that engineering antibodies with desired receptors binding properties requires a combination of the proper structural alterations (Canfield, p. 1490, second column, last paragraph). In so doing, Canfield also teaches gene constructs, as well as the antibody-based fusion proteins derived therefrom (see p. 1484, column 2, paragraphs 2-5). Thus, it would be obvious to one of ordinary skill in the art to create a construct to produce an engineered antibody-based fusion protein comprising a IgG4 CH2 domain and a variable region to create an antibody-based fusion protein that would have a greater circulating half-life *in vivo* than an antibody based fusion protein comprising an IgG1 CH2 domain linked to a non-Ig protein. One of ordinary skill in the art would reasonably expect success because Gillies created such an antibody-based fusion protein and Canfield taught engineered antibodies with desired receptor binding properties that require a combination of the proper structural alterations.). Thus, Grey would have appreciated what was well known in the art, that mutations to the Fc region can result in lengthened or improved serum half-lives.

Thus, the rejection of claim 27 as being unpatentable over Gillies (as stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*), in view of Gray (as stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*), as evidenced by Ravetch (as stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*), is maintained.

4. The rejection of claim 1 as being unpatentable over Gillies, in view of Gray et al., as evidenced by Winter is maintained, for the reason stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*). Insert statement of rejection. Applicant's arguments, see Remarks, filed 21 October 2005, with respect to the rejection of claim 1 as being unpatentable over Gillies (see *supra*) in view of Gray (see *supra*), as evidenced by Winter *et al.*, (U.S. Patent 5,624,821, hereinafter "Winter"), as stated in the Office Actions of 30 September 2004 and 21 June 2005, have been considered but are not persuasive.

Applicants argue that neither Gray nor Winter provide motivation to modify the construct of Gillies to incorporate specific mutations at positions 234, 235, 236, 237, or 297.

Winter specifically teaches alterations in binding affinity by substituting Leu for Glu235 in the mouse IgG2b CH2 domain (column 5, lines 42-58). By changing residue 235 (located in the critical CH2 hinge region), affinity for the human FCγ1R increased by over 100-fold. Winter specifically teaches that changes in this region could be used to produce altered antibodies more suited to a range of in vivo applications in man and other animals (column 5, lines 42-58). Gray et al. teach CLTA4IgG4 versus CTLA4IgG1 has decreased complement activation, which would result in a longer circulating half-life (column 10: lines 60-64). Gray also teaches that modifying the CH2 domain of Cγl , Cγ2, Cγ3 and Cγ4 is taught to reduce "a biological effector function... Fc receptor interaction" (column 4: lines 24-28).

Further, Applicants arguments are moot in light of the well-established teachings of Canfield *et al.*, (see discussion *supra*). Canfield teaches mutations in amino acids of the IgG CH2 domains in IgG1, -2., -3, and –4, and characterizes the binding affinities of those immunoglobulin domains with various FcγRs. Canfield teaches that substitution of either Leu(234) or Leu (235) in IgG1 and –3 are critical to high affinity binding. Substitution at either of those sites reduces the IgG association constant by 10-100 fold (see p. 1483, summary), as stated *supra*. Further, Canfield teaches that human IgG4 differs in the hinge-link region from the high affinity subclasses (IgG1 and IgG3) at only one position: Phe replaces Leu(234) (p. 1488, column 1, second full paragraph). Thus, it would be obvious to one of ordinary skill in the art to mutate the Leu(234) in an IgG1 or IgG3 Ch2 domain in order to reduce binding affinity. One of skill in the art would reasonably expect success because the substitution occurs naturally in IgG4 that results in greatly reduced binding affinity.

The rejection of claim 1 as being unpatentable over Gillies, in view of Gray et al., as evidenced by Winter is maintained for the reasons stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*).

5. The rejection of claim 4 as being unpatentable over Gillies and Gray, in view of Michaelson '856 is maintained for the reasons stated in the Office Actions of 30 September 2004, 21 June 2005. Applicant's arguments, see Remarks, filed 21 October 2005, with respect to the rejection of claim 4 as being unpatentable over Gillies et al. (see *supra*), in view of Gray et al. (see *supra*), in view of Michaelson *et al.*, (U.S. Patent 5,348,876, hereinafter "Michaelson '856"), as stated in the Office Actions of 30 September 2004 and 21 June 2005, have been considered but are not persuasive.

Claim 4 recites an antibody-based fusion protein for administration to a mammal comprising at least a portion of a CH2 domain linked to a non-Ig Protein where the CH2 domain is an IgG3 CH2 domain comprising a mutation or a deletion that reduces binding affinity for an Fc receptor (FcR) having a longer circulating half-life in vivo than antibody-based fusion protein without a mutation or deletion, wherein the mutation or deletion at one or more amino acids is selected from the group consisting of Leu281, Leu282, Gly283, Asn344, and Pro378.

Applicants argue that Gray does not teach that the mutations of his invention result in an immunoglobulin fusion protein with an improved serum half life, as discussed elsewhere in Applicants arguments. Applicants further argue that neither Gray nor Michaelson '856 provide motivation to modify the construct of Gillies to incorporate a mutation at positions 281, 282, 283, 344,or 378. Applicants arguments have been considered but are moot in view of the new grounds of rejection.

Gray teaches CLTA4IgG4 versus CTLA4IgG1 has decreased complement activation, which would result in a longer circulating half-life (column 10: lines 60-64). Applicants' arguments are moot in light of the well-established, art-known, teachings as evidenced by, for example, Canfield *et al.*, (see discussion *supra*) and Michaelson *et al.*, (JBC 10 Feb 1977; 252(3):883-889; hereinafter "Michaelson *et al.*") and exemplified by Gray et al.

For example, in 1991 Canfield *et al.*, taught mutations in amino acids of the IgG CH2 domains in IgG1, -2., -3, and –4, and characterizes the binding affinities of those immunoglobulin domains with various FcγRs. Canfield teaches that substitution of either Leu(234) or Leu (235) in IgG1 and corresponding regions of IgG3 are critical to high affinity binding. Substitution at either of those sites reduces the IgG association constant by 10-100 fold (see p. 1483, summary), as stated *supra*. Further, Canfield teaches that human IgG4 differs in the hinge-link region from the high affinity subclasses (IgG1 and IgG3) at only one position: Phe replaces Leu(234) (p. 1488, column 1, second full paragraph). Thus, it would be obvious to one of ordinary skill in the art to mutate the Leu(234) in an IgG1 or the corresponding regions of an IgG3 Ch2 domain in order to reduce binding affinity. One of skill in the art

would reasonably expect success because the substitution occurs naturally in IgG4 that results in greatly reduced binding affinity.

Additionally, in 1977, Michaelson *et al.*, showed that the primary structure of the hinge region of IgG3, included a 47-residue insertion in the IgG3 CH2 hinge sequence corresponding to Val215 of IgG1, thus making Leu234 of IgG1 the region of the amino acid sequence as Leu281 of IgG3. Similarly, Leu235, Gly236, and Asn297 of IgG1 correspond to Leu282, Gly 283, and Asn344 of IgG3. These sequence difference and corresponding regions have been well known in the art since that time. Thus, Applicants argument that neither Gray nor Michaelson provide motivation to modify the construct of Gillies to incorporation a mutation at position 281, 282, 283, 344 or 378 are not persuasive. These corresponding regions were well known in the art at the time the application was filed, as evidenced by Michaelson *et al.*, and mutations affecting corresponding amino acids were well-established by Canfield et al.,, and further supported by the teachings of Gray, as previously discussed, *supra*. Moreover, Gray teaches that mutations in the corresponding region result in a longer circulating half-life (column 10: lines 60-64), as cited in the previous Office Actions, see *supra*.

The rejection of claim 4 as being unpatentable over Gillies and Gray, in view of Michaelson '856 is maintained for the reasons stated in the Office Actions of 30 September 2004, 21 June 2005, and *supra*.

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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